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Functional Single Ventricle: Cardiorespiratory Response to Exercise

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The cardiorespiratory response to exercise was measured in 27 children with functional single ventricle. All 27 patients had a significant reduction in exercise time, work performed, maximal exercise heart rate, maximal oxygen uptake and systemic arterial blood oxygen saturation. The reduction in exercise performance increased with increasing age of the patients. All patients ventilated excessively at rest and during exercise.

This study documented the precise level of exercise intolerance in patients with functional single ventricle. The progressive deterioration in exercise performance with increasing patient age may lend credence to the concept that operation for physiologic correction of functional single ventricle should be considered during or before adolescence.

Patients with functional single ventricle probably have reduced exercise tolerance (1). Also, there is a clinical perception that exercise intolerance in patients with functional single ventricle increases with increasing age. To our knowledge, however, neither the degree of exercise intolerance nor increasing exercise intolerance with increasing age has been measured precisely. It is important to document the precise level of exercise tolerance in patients with functional single ventricle to fully appreciate the impact of new, complex surgical procedures for palliation or orthotopic correction of these complex cardiac anomalies (2).

This investigation answers the questions: 1) do patients with functional single ventricle have abnormal exercise tolerance, and 2) do these patients have age-related changes in exercise intolerance?

Methods

Patients. Patients older than 5 years of age with functional single ventricle evaluated at the Mayo Clinic between October 1981 and December 1982 were included in this study. The term single ventricle includes tricuspid atresia or univentricular heart or other forms of common ventricle. The diagnosis of functional single ventricle was established by cardiac catheterization or echocardiography in all cases and confirmed subsequently at operation in 23 of 26 patients. Values for ventricular end-diastolic pressure and ventricular shortening fraction were obtained from the patients' most recent cardiac catheterization (3.5 days*) and echocardiogram (1 day*).

Study protocol. All but three of the patients underwent spirometry before exercise testing. The forced vital capacity, forced expiratory volume in 1 second, the ratio of forced expiratory volume in 1 second to forced vital capacity and the maximal voluntary ventilation were obtained using a spirometer that met acceptable criteria (Snowbird).

The following indexes of cardiorespiratory function were recorded at rest and at each work load during exercise: heart rate, respiratory rate, electrocardiogram, blood pressure, oxygen consumption, carbon dioxide production, minute ventilation, tidal volume and systemic arterial blood oxygen saturation (Hewlett-Packard no. 47201A ear oximeter). The volume of pulmonary blood flow in 11 of the 27 patients was measured at rest (seated on the cycle ergometer) by an acetylene-helium rebreathing technique (3). Subjects breathed through a unidirectional valve (Rudolph 2700). Flow was obtained as expired gas passed through a pneumotachograph (Fleisch no. 3) connected to a pressure transducer (Validyne DP45). Volume was obtained by electronically integrating the flow signal. Mixed expired oxygen and carbon dioxide were obtained from sampling at a port

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*Median time interval between exercise test and cardiac catheterization or echocardiogram.

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placed at the distal end of a 6 liter mixing box. Gases were analyzed by a mass spectrometer (Centronic 200 MGA) that previously had been calibrated using gases analyzed by the Haldane technique. Four electrocardiographic leads were monitored at all times and a 12 lead electrocardiogram was recorded at rest and at each work load. Heart rate was computed by averaging five consecutive RR cycles on the electrocardiogram, recorded at a paper speed of 50 mm/s. For each patient, blood pressure was measured in the arm from which the highest blood pressure was obtained (two patients had previous bilateral Blalock-Taussig anastomoses, such that measurement of blood pressure was not possible). A programmable air compression cuff system (Narco Systems, PE-300) and a compression cuff of appropriate size were used (4). The ST segment elevation or depression was assessed in each lead at rest and during exercise. The ST segment change was measured from the J point to 60 ms after the J point (5). The electrocardiogram was observed for 10 minutes after exercise.

Exercise was performed on a previously calibrated cycle ergometer (Siemans-Elema 380 B) using the protocol described by James et al. (5). This is a 3 minute incremental cycle exercise protocol. One of three combinations of work loads are utilized based on the patient's body surface area. The patients pedaled at 60 to 70 rpm and were encouraged to exercise to exhaustion. The exercise test was terminated by the examiner if a potentially serious arrhythmia occurred or if systolic arterial blood pressure decreased more than 20 mm Hg.

Data analysis. Total work performed, maximal power, exercise time, oxygen consumption and heart rate and blood pressure at rest and during exercise were compared with the same indexes in 149 normal children and young adults previously reported by James et al. (5) using an identical exercise protocol. For each patient, the number of standard deviations from the predicted value for each index measured was computed by subtracting the predicted value from the observed value for each patient and dividing this difference by the standard deviation for that index among the normal group. Maximal predicted oxygen uptake was calculated on the basis of the patient's height (6).

Normal control subjects. Respiratory rate, minute ventilation, the ventilatory equivalent for oxygen and systemic arterial blood oxygen saturation were compared with those of 15 normal children studied in our laboratory. The 15 normal subjects included 10 boys and 5 girls who averaged 11.7 years, 47.9 kg, 152 cm and 1.4 m^2 in age, weight, height and body surface area, respectively.

Statistical analysis. When appropriate, we utilized either a paired or an unpaired *t* test, linear regression or Fisher's exact test to analyze the data, with a probability of less than 0.05 being statistically significant. A standard deviation greater than 1.6 for total work, exercise time, maximal power and rest and exercise heart rate and blood pressure from the predicted normal value was considered significant.

Results

Clinical features. The ages of the 27 patients (13 boys and 14 girls) ranged from 6.5 to 17 years (mean 12.9). Fifteen patients had tricuspid atresia, 11 had a univentricular heart and 1 patient had complete atrioventricular canal with common atrium, double-outlet right ventricle, pulmonary stenosis and anamolous pulmonary venous return. Of the 27 patients, 12 had a previous single systemic to pulmonary artery or Glenn anastomosis, 6 had two previous systemic to pulmonary artery or Glenn anastomoses and 1 patient had a pulmonary artery band placed. All operations were performed at least 1 year before exercise testing. One patient had associated complete atrioventricular block. We excluded his heart rate data from analysis.

The age and sex distribution of the 15 patients with tricuspid atresia was similar to that of the 11 patients with univentricular heart. There were no significant differences in rest and exercise indexes of cardiorespiratory function between the patients with tricuspid atresia and the patients with univentricular heart.

Pulmonary function at rest. Twenty-four of the 27 patients had rest spirometry performed. As a group, the mean ($\pm$ SD) maximal voluntary ventilation (percent predicted) was 90 $\pm$ 18%, the ratio of forced expiratory volume in 1 second to forced vital capacity was 91 $\pm$ 7 and forced vital capacity (percent predicted) was 77%. Forced vital capacity (percent predicted) was less than 80% in 12 of the 24 patients. In general, forced vital capacity was normal in patients without prior thoracotomy (5 of 7 patients), but in those with thoracotomy it was normal in only 4 of 17 patients.

Exercise capacity. All but one patient exercised to exhaustion. The maximal nature of the study was apparent clinically by audible ventilation and inability to maintain a pedaling frequency of 60 to 70 rpm. The exercise test was terminated in one patient when multiple premature ventricular complexes occurred. No patient had chest pain, syncope or other adverse effects from the exercise study.

Total work performed, maximal power attained and duration of exercise were reduced by an average of 2.3, 2.3, and 2.8 standard deviations from predicted values, respectively (Fig. 1). The maximal oxygen uptake ($\dot{V}O_{2\ max}$) as a ratio of predicted maximal oxygen uptake ranged from 24 to 58% (mean 40). With increasing age, there was a significant decrease in work performed ($p = 0.004$; $r = -0.54$), maximal power attained ($p = 0.002$; $r = -0.60$) and $\dot{V}O_{2max}$ as compared with predicted normal $\dot{V}O_{2max}$ ($p = 0.012$; $r = -0.48$) (Fig. 2).

Heart rate at rest ranged from 69 to 115 beats/min (mean 101) and was not different from the predicted normal heart

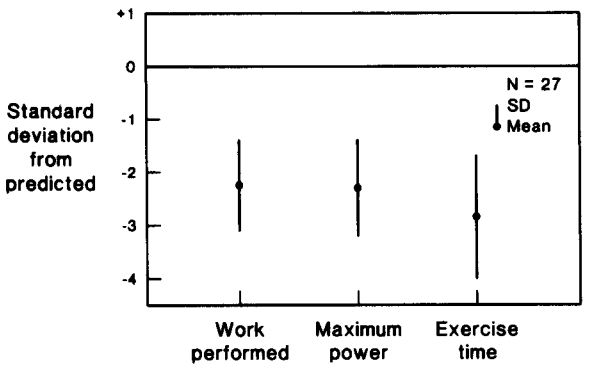


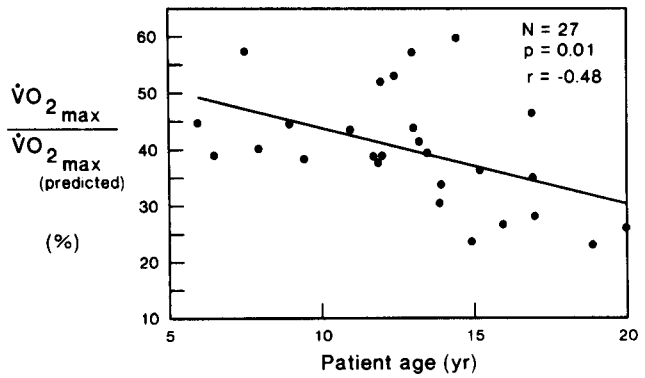
Figure 1. Standard deviations from predicted work performed, maximal power and exercise time.

rate at rest. The maximal heart rate during exercise ranged from 92 to 188 beats/min (mean 152) which was 3 standard deviations below the predicted normal maximal heart rate. Older patients ($p = 0.056$, $r = -0.39$) tended to have a greater reduction in maximal heart rate during exercise from the predicted normal maximal heart rate during exercise than did younger patients.

Blood pressure at rest (mean systolic 111 mm Hg, range 90 to 180; mean diastolic 69 mm Hg, range 50 to 85) and during exercise (mean systolic 141 mm Hg, range 90 to 275; mean diastolic 72 mm Hg, range 40 to 85) were not different from normal values. One patient had hypertension at rest (180/50 mm Hg) and during exercise (275/40 mm Hg), presumably related to a large systemic to pulmonary artery anastomosis (pulmonary blood flow = 4.7 liters/min per m^2) associated with a relatively low pulmonary artery resistance.

The average systemic arterial blood oxygen saturation was 83% (range 76 to 93) at rest, which decreased to 57% (range 38 to 81) during exercise. Both the rest and the exercise arterial blood oxygen saturation levels were reduced significantly ($p < 0.05$) from normal. Pulmonary blood flow at rest was measured in 11 of the 27 patients and ranged from 1.7 to 4.7 liters/min per m^2 (mean 2.9). There was a positive correlation between pulmonary blood flow at rest and systemic arterial blood oxygen saturation at rest ($p = 0.04$; $r = 0.62$). Furthermore, there was a significant correlation between systemic arterial blood oxygen saturation at rest and the ratio of maximal oxygen consumption and predicted maximal oxygen consumption ($p = 0.04$; $r = 0.39$) (Fig. 3) and between systemic arterial blood oxygen saturation at rest and exercise time ($p = 0.02$; $r = 0.45$). The higher a patient's rest systemic arterial blood oxygen saturation, the better the exercise performance.

Figure 2. Relation between patient age and reduction of predicted maximal oxygen consumption ($\dot{V}O_{2\,max}$) compared with the maximal predicted value.



The hemoglobin levels averaged 18.3 g/dl (range 15.9 to 23.4), and the hematocrit levels averaged 54.2% (range 44.6 to 70.1). There was a significant inverse relation between hematocrit and rest systemic arterial blood oxygen saturation ($p = 0.001$; $r = -0.59$) and between hematocrit and exercise capacity (the ratio of maximal oxygen consumption and predicted maximal oxygen consumption [$p = 0.03$; $r = -0.42$]). There was no significant ($p = 0.24$) relation between age and hematocrit or hemoglobin. However, in a large group of patients with single ventricle ($n = 42$; preliminary observation), there was a significant correlation ($p = 0.024$; $r = 0.347$) between age and hematocrit.

Measurements of left ventricular end-diastolic pressure for 22 of the 27 patients were available. Left ventricular end-diastolic pressure tended to be related positively to increasing age, but the trend was not statistically significant. Echocardiographic measurements of left ventricular shortening fraction were available in 13 of the 27 patients. There was no apparent relation between patient age and shortening fraction. There was a significant ($p < 0.05$; $r = -0.61$) correlation between left ventricular shortening fraction and left ventricular end-diastolic pressure for the 11 patients in whom both measurements were available. Reduced left ventricular shortening fraction was associated with elevated left ventricular end-diastolic pressure, and increased shortening fraction was associated with reduced left ventricular end-diastolic pressure. There was no apparent relation between work capacity (the ratio of maximal oxygen consumption and predicted maximal oxygen consumption) or systemic arterial blood oxygen saturation and either left ventricular end-diastolic pressure or left ventricular shortening fraction.

Exercise electrocardiography. Twelve of the 27 patients had arrhythmia before exercise, during exercise or within 10 minutes after exercise. A single or a maximum of two single premature ventricular complexes were observed in 4 of the 12 patients. One patient had premature atrial complexes after exercise. Of the 12 patients, 3 had multiple premature ventricular complexes or couplets before, during or after exercise and 4 had more than two single premature ventricular complexes. The exercise study was terminated for one patient who experienced multiple pre-

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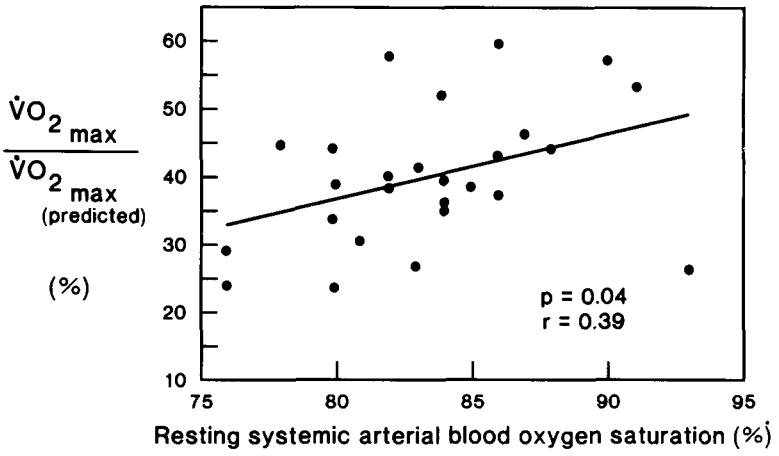


Figure 3. Relation between systemic arterial blood oxygen saturation at rest and maximal oxygen consumption ($\dot{V}O_{2\ max}$) as percent of the predicted value.

mature ventricular complexes during exercise. Only 1 of the 6 patients younger than 10 years of age had arrhythmia, whereas 11 of the 21 patients older than 10 years of age had arrhythmia. This difference was not statistically significant.

The ST segment change during exercise could be assessed accurately in 25 of the 27 patients. Eleven of the 25 patients had ST segment depression of 1 or more during exercise. ST segment depression during exercise was seen in 1 of the 6 patients younger than 10 years of age and in 10 of the 19 patients older than 10 years of age. This trend toward increased ST segment depression with increasing age was not statistically significant. There was no relation between depth of ST segment depression and either age or exercise performance.

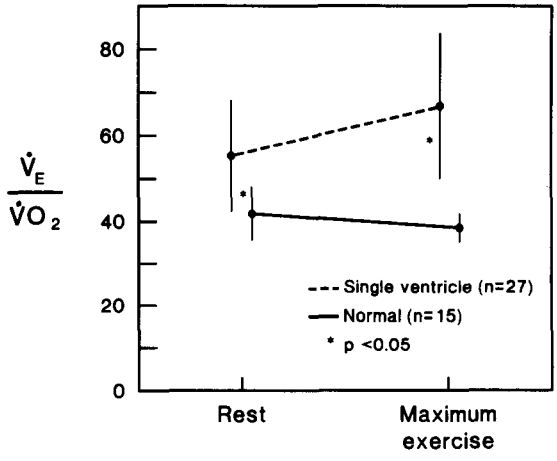
Exercise ventilation. The ventilatory equivalent for oxygen was significantly ($p < 0.05$) greater for patients with functional single ventricle than for control subjects, both at rest (single ventricle 55.3; control 41.8) and at maximal exercise (single ventricle 66.7; control 38.5) (Fig. 4). The increased ventilatory equivalent for oxygen resulted, in part, from abnormal increases in both respiratory rate and tidal volume. At maximal exercise, there was no significant difference in ventilation (as a percent of measured maximal voluntary ventilation at rest) between patients with functional single ventricle and control subjects. However, the similar ratios of ventilation to rest maximal voluntary ventilation were obtained at a significantly lower oxygen uptake in patients with functional single ventricle than in control subjects (Fig. 5).

Discussion

Although patients with functional single ventricle can be classified pre- and postoperatively by the New York Heart Association system, this type of subjective functional classification may be misleading. Several investigations (7–9) demonstrated that subjective estimates of exercise capacity in cyanotic children uniformly overestimate measured exercise capacity. Detailed exercise testing is necessary for an accurate assessment of functional capacity.

Exercise intolerance. Clinically, patients with functional single ventricle have exercise intolerance. To our knowledge, however, there have been no attempts to document the precise level. In this study, we demonstrated a large reduction from normal values in total work, exercise time and maximal oxygen uptake in 27 patients with functional single ventricle. In addition, we confirmed the clinical suspicion that the functional capacity of patients with functional single ventricle decreases with increasing age. The reductions from normal values in total work, maximal power, maximal exercise heart rate and ratio of maximal oxygen uptake to predicted maximal oxygen uptake were more pronounced with increasing patient age. Also, ST segment depression and arrhythmia tended to occur more frequently

Figure 4. Comparison of rest and exercise ventilatory equivalents ($\dot{V}_E$) for oxygen in 27 patients with functional single ventricle and 15 normal subjects. The **asterisks** refer to comparisons between normal subjects and patients with single ventricle. **Vertical bars** indicate standard deviations. $\dot{V}O_2$ = maximal oxygen consumption.



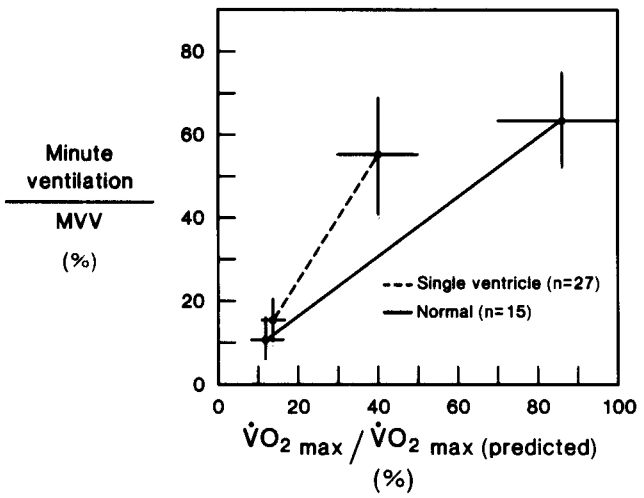


Figure 5. Comparison of rest and exercise minute ventilation as a percent of measured maximal voluntary ventilation (MVV) in 27 patients with functional single ventricle and 15 normal subjects. $\dot{V}O_{2\ max}$ = maximal oxygen consumption.

in patients who were older than 10 years of age than in patients younger than 10 years of age. The reason for this reduction in performance with increasing age is unclear. One might hypothesize that with increasing age, function of the chronically volume overloaded single ventricle deteriorates and the incidence and severity of atrioventricular valve regurgitation increases. Although left ventricular end-diastolic pressure tended to be related to age, this relation was not statistically significant. Age-related deterioration of ventricular function may, in part, explain the reduction in exercise capacity. However, our sample size may have been too small or our measurements of left ventricular function too crude to measure these changes precisely. None of the 22 patients had important atrioventricular valve regurgitation.

The level of arterial hypoxemia at which patients continued to exercise was striking. One patient stopped exercising only when the systemic arterial blood oxygen saturation reached 38%. As expected, there was a significant ($p = 0.04$; $r = 0.39$) (Fig. 3) direct relation between systemic arterial blood oxygen saturation at rest and exercise performance. Also, the systemic arterial blood oxygen saturation at rest was directly related to the quantity of pulmonary artery blood flow at rest. A positive correlation between exercise capacity and level of rest pulmonary artery blood flow and between exercise capacity and systemic arterial blood oxygen saturation has been demonstrated previously in cyanotic patients with tetralogy of Fallot (7).

Exercise heart rate response. The mean maximal exercise heart rate of 152 beats/min measured in our subjects was reduced. A reduction in maximal exercise heart rate was noted by Crawford and others (7–9) in patients with tetralogy of Fallot. The cause of this abnormally reduced maximal heart rate is unclear, but it may be explained on the basis of hypoxemia. Perfusion of the carotid body with hypoxic blood can cause bradycardia (10). Also, Åstrand and Åstrand (11) described relative bradycardia in subjects after acclimatization to high altitudes.

Exercise ventilation. Our patients had excessive ventilation at rest and exercise, which was manifested by a striking increase of the ventilatory equivalent for oxygen. In other investigations (8,9,12) similar observations were made in cyanotic patients with tetralogy of Fallot. In two of these three studies (8,9), the ventilatory equivalent for oxygen at maximal exercise was 52.6 and 52, respectively, as compared with 66.7 in our study. The higher value recorded in our study probably reflects increased levels of exercise performed by our patients as compared with those previously reported. The patients studied by Eriksson and Bjarke (9) exercised to 30% of predicted maximal oxygen uptake, while our patients exercised to 40%. The cause of the excessive ventilation probably is multifactorial. It has been noted that the ventilatory response to hypoxia is reduced in patients with cyanotic congenital heart disease(12,13). However, a recent study (14) demonstrated at least a partial response to hypoxia. Although we did not perform hypoxic ventilatory response tests in our patients, hypoxia as it occurred during exercise was, in several patients, associated with large increases in ventilation, and in other patients, an equivalent degree of hypoxia was associated with only modest ventilatory increases. Shephard (15) attributed hyperventilation at rest in patients with cyanotic congenital heart disease to true or relative hypercapnia. Increased dead space ventilation and an increased arterial-alveolar partial pressure of carbon dioxide P_{CO_2} gradient led Strieder et al. (16) to postulate that decreased ability to eliminate carbon dioxide in cyanotic congenital heart disease leads to excessive ventilation. If carbon dioxide cannot be eliminated efficiently, there is impaired compensation for metabolic acidosis resulting from carbon dioxide and lactic acid production. Our data support their conclusion. At the highest level of exercise, our patients were breathing at a percent of their maximal voluntary ventilation equivalent to that of normal subjects at maximal exercise. The ventilation-load relations were so steep that if an additional work load had been possible, ventilation would have met or exceeded maximal voluntary ventilation. Furthermore, though the minor reductions of forced vital capacity and maximal voluntary ventilation appear to be trivial at rest, an additional burden is placed on the already overworked ventilatory apparatus during exercise.

The forced vital capacity was abnormal in half of our patients. Crawford et al. (7) also found reduced forced vital capacity (< 80% of predicted) in 9 of their 13 patients. These reductions suggest the presence of restrictive lung disease, which could be a result of prior thoracotomy or pulmonary congestion, or both.

Implications. This study documented the precise level of exercise intolerance in patients with functional single ventricle. In addition, it demonstrated a decrease in exercise performance with increasing patient age. The age-related decrease in exercise performance may lend credence to the concept that operation for physiologic correction of tricuspid atresia and univentricular heart using the modified Fontan approach should be considered during or before adolescence.

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